Appendix 3
ALPHAGAN United Kingdom
and Ireland SPC

Preclinical safety data
The available mutagenicity and carcinogenicity data indicate that Alphagan® will not exert neither mutagenic nor carcinogenic activities under the conditions of clinical use.

PHARMACEUTICAL PARTICULARS

List of excipients
Benzalkonium Chloride (Preservative) 0.005% (0.05 mg/ml)
Polyvinyl alcohol 1.4% (14 mg/ml)
Sodium chloride
Sodium citrate, dihydrate
Citric acid, monohydrate
Purified water
Hydrochloric acid /or
Sodium hydroxide to adjust pH

Incompatibilities
Physical and chemical incompatibilities have not been observed.

Shelf life
Alphagan® has a shelf life of 36 months in the unopened 5ml container. Use within 28 days after first opening.

Special precautions for storage
Alphagan® should be stored at or below 25°C (77°F).

Nature and contents of container
White low density polyethylene dropper bottles with a 35 microlitre tip. The cap is either a conventional screw cap or a Compliance Cap (C-Cap).

Alphagan® is available as 5ml packs.

Instructions for use/handling
None.

MARKETING AUTHORISATION HOLDER

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Allergan Limited,
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IRELAND
Allergan Pharmaceuticals (Ireland),
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18th March 1997 (UK), 14th November 1997 (Ireland)

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November 1997

ACAI140-97

Alphagan®▼ (brimonidine tartrate ophthalmic solution) 0.2%

Summary of Product Characteristics

NAME OF THE MEDICINAL PRODUCT
Alphagan®

QUALITATIVE AND QUANTITATIVE COMPOSITION
Brimonidine tartrate 0.2% (2.0 mg/ml)
(equivalent to brimonidine base 0.13%, 1.3 mg/ml)
1 drop of Alphagan® = approximately 35 µl = 70 µg brimonidine tartrate

PHARMACEUTICAL FORM
Eye drops, solution.

CLINICAL PARTICULARS

Therapeutic indications
Alphagan® may be used as monotherapy for the lowering of intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension, who are known, or thought likely to be intolerant of topical betablocker therapy and/or in whom topical betablocker therapy is contraindicated. Alphagan® may be used as adjunctive therapy when IOP is not adequately controlled by a topical beta-blocking agent.

Posology and method of administration
The recommended dose is one drop of Alphagan® in the affected eye(s) twice daily, approximately 12 hours apart. No dosage adjustment is required for use in elderly patients.

If more than one topical ophthalmic drug is to be used, the different drugs should be instilled 5-15 minutes apart.

Alphagan® has not been studied in patients with hepatic or renal impairment - see **Special warnings and special precautions for use.**

The safety and effectiveness of Alphagan® in children have not been established.

Contra-indications
Alphagan® is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. Alphagan® is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

Special warnings and special precautions for use
Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease.

Some (12.7%) patients in clinical trials experienced an ocular allergic type reaction with Alphagan® (see **Undesirable effects** for details). If allergic reactions are observed, treatment with Alphagan® should be discontinued.

Alphagan® should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Alphagan® has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

The preservative in Alphagan®, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft (hydrophilic) contact lenses should be instructed to wait at least 15 minutes before inserting soft contact lenses after instilling Alphagan®.

Interaction with other medicaments and other forms of interaction
Although specific drug interaction studies have not been conducted with Alphagan®, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

No data on the level of circulating catecholamines after Alphagan® administration are available. Caution, however, is advised in patients taking medications which can affect the metabolism and uptake of circulating amines e.g chlorpromazine, methylphenidate, reserpine.

After the application of Alphagan®, clinically insignificant decreases in blood pressure were noted in some patients. Caution is advised when using drugs such as antihypertensives and/or cardiac glycosides concomitantly with Alphagan®.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin).

Pregnancy and lactation
The safety of use during human pregnancy has not been established. In animal studies, brimonidine tartrate did not cause any teratogenic effects. In rabbits, brimonidine tartrate, at plasma levels higher than are achieved during therapy in humans, has been shown to cause increased preimplantation loss and postnatal growth reduction. Alphagan® should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

Use during lactation
It is not known if brimonidine is excreted in human milk.

The compound is excreted in the milk of the lactating rat. Alphagan® should not be used by women nursing infants.

Effects on ability to drive and use machines
Alphagan® may cause fatigue and/or drowsiness, which may impair the ability to drive or operate machinery.

Undesirable effects
Ocular effects
The most frequently reported ocular adverse events (in descending order of incidence) were ocular hyperaemia, ocular burning/stinging, blurring, foreign body sensation, conjunctival follicles, ocular allergic reactions and ocular pruritus. Some patients experienced several of these symptoms and/or signs which collectively were considered to be an ocular allergic reaction. This occured in 12.7% of subjects (causing withdrawal in 11.5% of subjects in clinical trials) and the onset was between 3 and 9 months in the majority of patients. Where data are available in subjects who withdrew from the studies due to ocular allergic reactions, all the symptoms resolved without long term sequelae upon discontinuation of therapy.

Ocular events occurring occasionally included: corneal erosion/staining, photophobia, eyelid hyperaemia, ocular ache/pain, ocular dryness, tearing, eyelid oedema, conjunctival oedema, blepharitis, conjunctival blanching, ocular irritation, abnormal vision, conjunctival discharge and conjunctivitis.

Systemic effects
The most frequently reported systemic effects were oral dryness, headache and fatigue/drowsiness.

Occasional reports included upper respiratory symptoms, dizziness, gastrointestinal symptoms, asthenia and abnormal taste.

Rarely reported systemic events included depression, systemic allergic reaction, nasal dryness and palpitations.

Overdose
Ophthalmic overdose:
There is no experience with the unlikely case of an overdosage via the ophthalmic route.

Systemic overdose resulting from accidental ingestion:
No incidences of human ingestion of Alphagan® are known. Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, respiratory depression and seizur

No clinical signs were observed at the 2mg base/kg dose level using 0.2% brimonidine tartrate orally in mice and rats. This dose is equivalent to a total of 15ml of Alphagan® consumed by a 10 kg child.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Brimonidine is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoreceptor.

This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Topical administration of brimonidine tartrate decreases intraocular pressure (IOP) in humans with minimal effect on cardiovascular or pulmonary parameters. Limited data are available for patients with bronchial asthma showing no adverse effects.

Alphagan® has a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing. In two 1 year studies, Alphagan® lowered IOP by mean values of approximately 4-5 mmHg.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. It is thought that Alphagan® may lower IOP by reducing aqueous humour formation and enhancing uveoscleral outflow.

Pharmacokinetic properties
General characteristics
After ocular administration of a 0.2% solution twice daily for 10 days, plasma concentrations were low (mean Cmax was 0.06 ng/ml). There was a slight accumulation in the blood after multiple (2 times daily for 10 days) instillations. The area under the plasma concentration-time curve over 12 hours at steady state (AUC0-12h) was 0.31 ng·hr/ml, as compared to 0.23 ng·hr/ml after the first dose. The mean apparent half-life in the systemic circulation was approximately 3 hours in humans after topical dosing.

The plasma protein binding of brimonidine after topical dosing in humans is approximately 29%.

Brimonidine binds reversibly to melanin in ocular tissues, in vitro and in vivo. Following 2 weeks of ocular instillation, the concentrations of brimonidine in iris, ciliary body and choroid-retina were 3- to 17-fold higher than those after a single dose. Accumulation does not occur in the absence of melanin.

The significance of melanin binding in humans is unclear. However, no significant ocular adverse reaction was found during biomicroscopic examination of eyes in patients treated with Alphagan® for up to one year, nor was significant ocular toxicity found during a one year ocular safety study in monkeys given approximately four times the recommended dose of brimonidine tartrate.

Following oral administration to man, brimonidine is well absorbed and rapidly eliminated. The ma part of the dose (around 75% of the dose) was excreted as metabolites in urine within five days; no unchanged drug was detected in urine. In vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism.

Kinetics profile:
No great deviation from dose proportionality for plasma Cmax and AUC was observed following a single topical dose of 0.08%, 0.2% and 0.5%.

Characteristics in patients
Characteristics in elderly patients:
The Cmax, AUC, and apparent half-life of brimonidine are similar in the elderly (subjects 65 years or older) after a single dose compared with young adults, indicating that its systemic absorption and elimination are not affected by age.

Based on data from a 3 month clinical study, which included elderly patients, systemic exposure to brimonidine was very low.